PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 230875	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/035050	International filing date *(day/month/year)* 22.10.2004	Priority date *(day/month/year)* 22.10.2003
International Patent Classification (IPC) or national classification and IPC C07D487/04, A61K31/551, A61P31/00		
Applicant GOVERNMENT OF THE UNITED STATES OF AMERICA...		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.02.2005	12.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baston, E Telephone No. +49 89 2399-

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International application No.
PCT/US2004/035050

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-50 as originally filed

   Claims, Numbers

   1-80 as originally filed

   Drawings, Sheets

   1/13-13/13 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 49-61 "with respect to industrial applicability"

because:

☒ the said international application, or the said claims Nos. 49-61 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-80
	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-80
Industrial applicability (IA)	Yes:	Claims	1-48,62-80
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Section III

Claims 49-61 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Section V

The following documents were cited in the search report and were considered for the examination of the present application:

D1: THURSTON D E ET AL: "Synthesis of Sequence-Selective C8-Linked Pyrrolo(2,1-c)(1,4)benzodia zepine DNA Interstrand Cross-Linking Agents" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 61, no. 23, 1996, pages 8141-8147,

D2: SAGNOU, MJ. ET AL.: "Design and Synthesis of Novel Pyrrolobenzodiazepine (PBD) Prodrugs for ADEPT and GDEPT" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 10, 2000, pages 2083-2086,

D3: GREGSON S J ET AL: "SYNTHESIS OF A NOVEL C2/C2'-EXO UNSATURATED PYRROLOBENZODIAZEPINE CROSS-LINKING AGENT WITH REMARKABLE DNA BINDING AFFINITY AND CYTOTOXICITY" CHEMICAL COMMUNICATIONS - CHEMCOM, ROYAL SOCIETY OF CHEMISTRY, GB, no. 9, 1999, pages 797-798,

D4: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09),

D5: GREGSON S J ET AL: "Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, 2004, pages 1161-1174.

The priority document of the present application is not yet available. In case that the presently claimed subject matter is not fully supported by the priority document, D5 might be relevant for the assessment of novelty and / or inventive step in the national / European phase.

D6: GREGSON S J ET AL: "Design, Synthesis, and Evaluation of a Novel Pyrrolobenzodiazepine DNA-Interactive Agent with Highly Efficient Cross-Linking Ability and Potent Cytotoxicity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 5, 2001, pages 737-748.

The present appliation is directed to dimeric pyrrolobenzodiazepines, which are considered to be useful for the treatment of cancer or Alzheimer's disease. This effect is believed to be due to the ability to recognize and bind to specific sequences of DNA.

Dimeric pyrrolobenzodiazepines are known from the cited documents of the prior art (compare e.g. D4, figure 11-14 or figure 17). The presently claimed compounds can be distinguished from this document by the presence of groups X and Y. Some compounds falling under the scope of claims 1 and 3 are known from documents D1 (scheme 1) and D2 (scheme 2) and thus novelty cannot be acknowledged (Art. 33(2) PCT.

The proviso in claim 2 is obviously directed at the exclusion of specific compounds known to the Applicant, the relevant prior art should be incorporated in the description (cf. Rule 5.1 PCT) and if said prior art was published before the relevant priority dates of the present application and relates to compounds having a similar utility to the compounds of the present application, it will also be necessary to show that the compounds claimed solved the problem as stated above vis-à-vis these compounds.
Document D2 also deprives the novelty of claim 2, since the combination of X,Y= hydroxy and R^1,R^2,R^5,R^6=H are not excluded from this claim.
Document D3 anticipates a compound (ex. 18), which carries on both nitrogens a substituent. Document D1 only refers to a compound with a OCD_3 group and thus only partly explains the disclaimer in claim 2.

The description contains various tests which show the cytotoxic properties of some congeners of the presently claimed general formulae. However e.g. from document D2 a compound (example 16) was known which can be distinguished from example 16 of the present application (figure 1G) only by the presence of the terminal methylene groups. This structure is characterized by the presence of two hydroxy groups for x and y. Furthermore claims 1-3 encompass for x and y various groups, which are considered to be the most crucial structural difference in comparison to the prior art. However no

comparative data are presented which show any effects of these groups. Moreover the breadth of these definitions is not justified in view of the low number of examples presented and in view of the high structural resemblance in comparison to compounds from the prior art. The involvement of an inventive step is not acknowledged (Art. 33(3) PCT).

Claims 49-61 at least in part define the scope of protection with unclear expressions like "growth of a cell" or "hyperproliferation" which need to be replaced by well defined diseases (Art. 6 PCT).

For the assessment of the present claims 49-61 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.